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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,269	09/16/2002	Olli P. Kallioniemi	4239-62295	8794

36218 7590 05/25/2007

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EXAMINER	
DEJONG, ERIC S	
ART UNIT	**PAPER NUMBER**
1631	

MAIL DATE	DELIVERY MODE
05/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,269	KALLIONIEMI ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-11,13-40,64,67 and 68* is/are pending in the application.

4a) Of the above claim(s) *15-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-11,13,14,64,67 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicants response filed 03/12/2007 is acknowledged. Claims 1-5, 9-11, 13, 14, 64, 67, and 68 are currently under examination. Claims 6-8, 12, 41-63, 65, and 66 are canceled. Claims 15-40 are withdrawn.

Claim Rejections - 35 USC § 112

The rejection of claims 1-5, 9-11, 13, 14, 64, and 67 under 35 U.S.C. § 112, second paragraph, as being indefinite is withdrawn in view of applicants arguments and amendments made to the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-11, 13, 14, 64, and 67, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Kahn et al. (Cytometry et al. (1997) Vol. 28, pages 269-279).

The instant claims are drawn to a computer implemented method for counting nucleic acid probe signals in a multi-cell region of interest in a biological spectrum comprising, obtaining a plurality of successive two dimensional image slices of said region taken at different depths along a z-axis via confocal microscopy, distinguishing

spatially overlapping nucleic acid probe signals, automatically counting a number of test signals from a test probe, automatically counting a number of reference probe signals, and determining a ratio of the automatically-counted test signals to the automatically counted reference signals.

Kahn et al. sets for the visualization and localization of specific DNA sequences performed by fluorescence in situ hybridization (FISH) using laser scanning confocal microscopy and Factor Analysis of Biomedical Image Sequences (FAMIS) (see Kahn et al., Abstract). The methodology is disclosed as being computer-implemented as image analysis of convention 3D reconstructions of cells were obtained by means of the Image Space software (see Kahn et al., page 277, col. 1, lines 4-14). Kahn et al. sets forth obtaining both sample analysis and construction 3D image of a sample region by collecting a series of 2D of fluorescence images at different sample depths (see Kahn et al. Figures 1A-C, page 227, col. 1, line 5 though page 278, col. 1, line 18 and page 278, col. 1, line 45 through col. 2, line 5). Figure 1C of Kahn et al. sets forth that 2D fluorescence images were obtained at different confocal plants along the z-axis. Kahn et al., and further demonstrates that overlapping fluorescent signals may be distinguished from successive 2D images taken at different sample depths by use of a factor profiles a(i), b(i), and c(i), wherein said factor profiles were derived from 2D images obtained at different sample depths. Kahn et al. further sets forth the use of two fluorescent dyes, Fast Red (FR) and Thylozine Orange (TO) as probe labels, wherein said dyes may be used simultaneously (see Kahn et al., page 269, col. 1, line 5 through page 271, col. 2, line 4). FR is disclosed as providing a high quantum yield and was relied upon by Kahn

et al. to detect small amounts of DNA sequences in individual cells, which reads on the instantly claimed limitation of a test signal from a test probe. TO was relied upon to counterstain nuclei, which reads on the instantly claimed reference signals from a reference probe. Signals from both FR and TO fluorescently labeled probes are determined from each 2D image sequence and relied upon in the FAMIS application (see Kahn et al., page 273, col. 2, line 11, through page 275, col. 1, line 14).

Kahn et al. further teaches that problems previously resulting from the superposition of fluorescein signals, autofluorescence, and propidium iodide-stained nuclei are resolved when FR and TO spectral features are taken into account by FAMIS (see Kahn et al., page 278, col. 1, lines 20-31 and page 278, col. 2, line 22 through page 279, col. 1, line 18). Kahn et al. sets forth that although TO and FR distributions cannot be distinguished in any single 2D image, FAMIS decomposition of a plurality of 2D image sequences into specific TO and FR distributions permits a multispectral analysis. FAMIS decomposition of a plurality of 2D image sequences results in the generation of factor profiles involves transforming contiguous signals, obtained from successive 2D images, into a single curve that allows for determining which of the successive 2D images contains the strongest probe/reference signal. Direct comparison of decomposed TO and FR distributions obtained from 2D images involves the determination of a ratio of TO and FR intensities, which reads on determining a ratio of counted test signals from the test probe and counted reference signals from the reference probe. Further, all comparison of TO and FR fluorescence intensity were performed without reference to either the boundaries of a cell nucleus or of a cell.

Regarding image analysis and the decomposition of images, Kahn et al. sets forth that iterative algorithms are applied by FAMIS in the analysis and computation of combined 2D images into a clustered matrices, which reads on the instantly instant limitations of automatically counting a number of test signals and automatically counting a number of reference signals.

Response to Arguments

Applicant's arguments filed 03/12/2007 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 U.S.C. 102(b) as being anticipated by Kahn et al., applicants argue that Kahn's description of iterative algorithms does not anticipate automatically counting a number of test signals or automatically counting a number of reference signals as recited in the instant claims. Applicants further argue that it requires impermissible hindsight to conclude that "factors with physical meaning" discloses counting signals as recited in the instant claims and Kahn's description could mean any number of arrangements other than counting.

In response, the computer implemented application of factor analysis (FAMIS) disclosed by Kahn et al. summarizes image sequences into a reduced number of images, called factor images, and curves called factors (see especially Kahn et al., page 273, col. 2, lines 9 through page 275, col. 1, line 13). FAMIS is taught as being applied to improve focus and to determine the location of fluorescent probes of FISH preparations by means of 3D emission patterns. Further, Kahn et al. explicitly teach the

visualization of each "spot" and nucleus background. Therefore, the teachings of Kahn et al. anticipate the limitation of automatically counting a number of test signals or automatically counting a number of reference signals as instantly claimed. Further, applicants argument regarding impermissible hindsight is not germane to the instant rejection based on the anticipation of the instant claims by Kahn et al. under 35 USC §102(b).

Applicants further argue that Kahn et al. fails to anticipate determining a ratio of automatically-counted test signals from the test probe to the automatically-counted reference signals from the reference probe. Applicants acknowledge that Kahn et al. does mention intensities in a number of places, but further argue that determining a ratio of intensities would not anticipate determining a ratio for counted signals.

In response, it is reiterated from the above rejection that Kahn et al. discloses the decomposition of a plurality of 2D image sequences results in the generation of factor profiles involves transforming contiguous signals, obtained from successive 2D images, into a single curve that allows for determining which of the successive 2D images contains the strongest probe/reference signal. Direct comparison of decomposed TO and FR distributions obtained from 2D images involves the determination of a ratio of TO and FR intensities, which reads on determining a ratio of counted test signals from the test probe and counted reference signals from the reference probe. Further, comparison of fluorescent intensities derived from observed (counted) fluorescent labels in a sample under investigation reads on determining a ration for counted signals as

instantly claimed. Neither the instant claims not the instant disclosure set forth a definition for "determining a ration for counted signals" that would exclude embodiments wherein a ratio of intensities is determined for said counted signals. Absent an explicit definition, terms recited in the instant claims are afforded their plain meaning in the art. See MPEP §2111.01.

Applicants further argue that Kahn makes no mention of distinguishing overlapping signals as recited in the instant claims and points out that the instant claims explicitly recite "distinguishing spatially overlapping nucleic acid probe signals". Applicants argue that Kahn et al. would lead on of ordinary skill in the art to a solution that does not involve distinguishing spatially overlapping nucleic acid probe signals because it describes a solution with factors that "do not depend of spatial locations".

In response, it is first noted that the computer implemented application of factor analysis (FAMIS) is not independent of spatial locations of observed fluorescent signals. It is further reiterated from the above rejection that Kahn et al. explicitly teaches that problems previously resulting from the superposition of fluorescein signals, autofluorescence, and propidium iodide-stained nuclei are resolved when FR and TO spectral features are taken into account by FAMIS. Further, Kahn et al. explicitly teach that the problem of superposition of signals from FR and TO nuclei can be solved when photobleaching is taken into account by FAMIS to distinguish two dynamic patters resulting from TO fast photobleaching and FR very slow photobleaching (see especially Kahn et al., page 278, col. 2, lines 23-39).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shukla Ram can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric S DeJong
Examiner
Art Unit 1631

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER